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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/655,815	09/06/2000	Robert Lanza	P 0275705 23523-0162	8460

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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 03/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/655,815	LANZA ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *15-19,29-32 and 49-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,20-28,33 and 38-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-55 are pending.

Claims 1-14, 20-28, 33 and 38-48 are under current examination.

Election/Restrictions

Claims 15-19, 29-32, 34-37 and 49-55 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected groups, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code, see p. 7, line 14. See MPEP § 608.01. Appropriate correction is required.

A substitute specification excluding the claims is required pursuant to 37 CFR 1.125(a) because the margins of the instant specification are not in correct margin format and hole-punching has eliminated some of the text.

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional

subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

The disclosure is objected to because of the following informalities:

p. 4, line 31 states, "histocompatibiliy." It is suggested that this be rewritten to state, "histocompatibility."

p. 9, line 17 states, "copending Application Serial No." yet no serial number is listed.

p. 15, line 8, states, "The disclosure of U.S. application Serial No." yet no serial number is listed.

p. 23, line 10 states, "using he avidin-biotin detection system." It is suggested this be rewritten to state, "using the avidin-biotin detection system."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim1-14, 20-28 and 33 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to a method of testing immune compatibility of cloned cells of tissues in an animal model comprising obtaining a cell from a donor animal, transferring the nucleus from the cell into a recipient oocyte or other suitable recipient cell to generate an embryo, isolating an embryo having at least one cell, an embryonic disc, and/or stem cell from said embryo, injection the embryo, disc, and/or stem cell into a donor animal at the same time as a control embryonic disc and/or stem cell; and examining the injection sites for teratoma formation. In further embodiments, the claimed invention is directed to a method for generating immune compatible tissues for transplantation comprising obtaining a donor cell from an intended transplant recipient, transferring the nucleus from said cell into a recipient oocyte or other suitable cell to generate an embryo or fetus, isolating from the embryo or fetus a cell of the type required for transplantation, and engineering a tissue from the cells.

The specification teaches a method for engineering cloned, immune compatible, developmentally differentiated cells into tissues for transplantation, and methods of using such tissues to treat a patient in need of a transplant (see p.

3, lines 10-19), and a method for testing the immune compatibility of cloned tissues or cells in an animal model (see p. 5). The specification teaches that the described method would employ nuclear transfer and injection of an embryonic disc/inner cell mass and/or stem cell from the resulting embryo into a donor animal, and isolation of the resulting teratoma (see p. 5). The specification teaches that the animal model that would be preferred for generation of teratomas and studying immune compatibility is an ungulate, and preferably a bovine (see p. 6, lines 27-29). The specification teaches that typically, mitochondrial peptides displayed at the cell surface can serve as histocompatibility antigens (see p. 4, bridging paragraph). The specification teaches that foreign mitochondria would expected to result in rejection of therapeutic technology, however, using the claimed method, it has been found that cells having allogeneic mitochondria were not rejected when transplanted into the nuclear donor.

In particular, the specification teaches a method for testing immune compatibility of nuclear-transfer generated cells into cattle. The specification teaches that fibroblasts used for nuclear transfer were obtained from Holstein steers and a plasmid that expresses a reporter gene encoding enhanced green fluorescent protein was transfected into the isolated fibroblasts. Isolated embryos having at least one cell, or embryonic discs/inner cell mass (ICM) or stem cells generated from bovine blastocysts/stem cells were then injected into the paralumbar fascia of donor steers (two sites with the experimental (same animal) stem cells, two

cites with experimental (same animal) embryonic discs, two sites with inner cell mass, and four sites with control (different animal) stem cells). After two months, the muscle is examined for teratoma formation and tumors are histologically analyzed. The specification teaches that it is expected that the "same animal" stem cells would survive in the recipient (donor of the nucleus) animal in contrast to "different animal" stem cells. (See Example 1). The specification further teaches that in order to test teratoma formation in an immune-compromised model, ES cells were transfected with GFP derived from two Holstein steers and ICMs were derived from 12-day old blastocysts. The cells were then cut into pieces and preferably 100 microliters were loaded into a 1 ml syringe, and the ICMs were mechanically isolated and 100-150 microliters were loaded into a 1 ml syringe. The cells and ICMs were injected into the hind leg of SCID mice and two of the mice exhibited a small modular lesion (teratoma) after 7-8 weeks post-injection. This teratoma showed epithelial and stromal cells, but no evidence of cartilage, bone or adipose tissue (see Example 2). The specification further describes a method for the engineering of tissues for use in animal models as described in Example 2, where the teratomas are removed and various cell types are then isolated and grown in culture so that a variety of tissues may be generated from the cloned cells. Particularly, cells from bovine kidney, heart, skeletal muscle, cartilage, and skin were harvested from cloned and control fetuses. These cells were further expanded *in vitro* culture and the cells were then implanted with polymer scaffolds into the

dorsal subcutaneous space of athymic mice, or in the flank subcutaneous space of a steer. Tissues from the animals were then analyzed immunocytochemically and histochemically (see Example 3). It was found that there was extensive vascularization throughout the implants and the presence of multinucleated giant cells surrounding the polymer fibers.

It is noted that claims are directed to the formation of a nuclear transfer unit. It is well-known in the nuclear transfer art that steps such as oocyte-cell/nuclear membrane fusion, and activation of the resulting nuclear transfer unit must take place in order to effect embryogenesis; however, the claims do not provide such steps. To this end, the claimed methods of testing the immune compatibility and methods of providing a patient in need of a transplant, which require a nuclear transfer unit, would not be predicted to result in a successful nuclear transfer.

Furthermore, the claims are directed to a recipient oocyte or other suitable recipient cell [see claim 1, part (b), for example]. It is noted that it is well-known in the art that recipient cells that are commonly used for nuclear transfers are oocytes arrested at metaphase II; and further, the recipient oocyte would have to be enucleated for the nuclear transfer technique to be successful.

Some embodiments of the claimed invention are directed to methods for testing immune compatibility of cloned cells or tissues in an animal model. The specification broadly discusses methods of testing immune compatibility (see p. 7, lines 1-9, for example). The specification discusses a method to test immune

compatibility in nuclear transfer-generated cells in cattle (see Example 1). However, the specification does not provide sufficient teaching or guidance to show how the cattle carrying the teratomas would be tested for immune compatibility. The specification broadly discusses that the teratomas would be, "removed for histological analysis" (see p. 17, lines 26-27), but there is no particular guidance or working examples provided by the specification to show how these tissues would be analyzed and tested for immune compatibility. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. Although the specification provides a hypothesis (the specification teaches that it is expected that the "same animal" stem cells would survive in the recipient (donor of the nucleus) animal in contrast to "different animal" stem cells, see p. 18, lines 6-11), the specification does not provide particular teaching or guidance to show how the claimed method would be used to test immune compatibility, and as such, undue experimentation would have been required to implement the claimed methods.

Further embodiments of the claimed invention are directed to methods of providing a patient in need of a transplant with an immune compatible transplant (see claim 20, for example), however, the specification is not enabling for these methods. The specification teaches that cloned fetal bovine cells were used for implantation in athymic mice [see Example 2], however, the specification does not teach engineering tissues using cells isolated from a teratoma. It is noted that

teratomas, by definition are, "A neoplasm composed of multiple tissues, including tissues not normally found in the organ in which it arises." [See Stedman's Medical Dictionary, 1995]. And further, a neoplasm, by definition is, "An abnormal tissue that grows by cellular proliferation more rapidly than normal and continues to grow after the stimuli that initiated the new growth cease. Neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissue, and usually form a distinct mass of tissue which may be either benign (benign tumor) or malignant (cancer) new growth, tumor." [See Stedmans' Medical Dictionary, 1995]. As such, it is unclear how using cells isolated from a teratoma could be used to generate tissues that could be used in cellular transplantation, as the teratoma cells are considered abnormal and would continue to grow without structural organization. The specification teaches implantation of cloned bovine fetal cells, however, there is no guidance, teaching or working examples provided by the specification to show that the implantation of tissues or cells engineered from teratomas would indeed function as a transplant for a patient in need, as the claimed methods require [see, for example, claim 20], as such, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Some embodiments of the claimed invention [see claims 8-10] are directed to a heterologous gene which encodes a protein that is secreted, wherein the protein generates an immune response and the protein is a therapeutic protein. However,

the specification does not provide an enabling disclosure to show with particularity that any protein, to the breadth claimed, would generate an immune response or would be therapeutic. Furthermore, as the claims encompass a broad range of proteins, it would not be predictable as to which particular proteins would generate an immune response, or would be considered therapeutic.

Furthermore, it is noted that many unpredictable factors complicate cellular transplantation. Inverardi *et al.* (**Transplant Biology**, 1996) review the state of the art of cell transplantation and discuss various factors that affect successful cellular transplantation, such as problems of cell isolation and purification, cellular environment, the immune response to transplanted cells, as well as the preservation of cells used in cellular transplantation (see pp. 679-681). Inveradi *et al.* further review various clinical applications for cellular transplantation, each with varying results (see pp. 681-684). Inverardi *et al.* discuss the genetic engineering of cells to be used in cellular transplantation, and discuss the limitations of currently available gene delivery systems (see p. 685).

Accordingly, in view of the specification's lack of teaching or guidance for the use of any other recipient cell other than an enucleated oocyte in nuclear transfer, as well as the requirement for activation of the nuclear transfer unit to produce a successful nuclear transfer, the lack of guidance or working examples provided by the specification to show that implantation of tissues engineered from cells isolated from a teratoma would be therapeutic in an individual, as well as the lack of

guidance or working examples provided by the specification for methods of testing immune compatibility, it would have required undue experimentation for one skilled in the art to carry out the claimed methods.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 21, 22, 29, 30 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, as written, is incomplete. It is unclear how examining the injection sites for teratoma formation in part (e) of the claim, relates to the preamable, "A method of testing the immune compatibility of cloned cells or tissues in an animal model." Clarification and/or amendment is requested. Claims 2-14 depend from claim 1.

Claim 1, as written, is confusing. The claim states the transferring of the nucleus from a donor cell into a recipient oocyte or other suitable recipient cell. It is not clear what, "other recipient cell" encompass, as it is well-known in the nuclear transfer art that the recipient cell is typically an enucleated oocyte. Claims 2-14 depend from claim 1.

Claim 9, as written is vague. The claim states that the protein is a therapeutic protein. However, the term, "therapeutic" is not defined by the claim. Furthermore, it is not clear what the protein would be therapeutic for (e.g. a particular disease?). Clarification and/or amendment is requested.

Claim 21 recites the term, "skid" mouse in line 2 of the claim; however, the term, "skid" is not defined by the claim. It is suggested that this term be substituted with, "scid". Clarification and/or amendment is requested.

Claim 22 recites the limitation "said intended transplant recipient" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 29 recites the limitation "said animal" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 30 depends from claim 29.

Claim 33 recites the limitation "said intended transplant recipient" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 48, as written, is confusing. The claim refers to the teratoma of claim 48, in line 1 of the claim. Clarification and/or amendment to the claim is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 38, 42, 44, 45, 46 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Anderson *et al.* (**Ani Reprod Sci**, Vol. 45, 1996, pp. 231-240).

Note that claims 44, 45, 46 and 47 are product by process claims. See MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Claim 38 is directed to an animal containing at least one teratoma. Claim 42 is directed to the animal of claim 28, wherein the teratoma is not rejected by the animal's immune system. Claim 44 is directed to a teratoma isolated from the animal of claim 38. Claim 45 is directed to the teratoma of claim 44, wherein the teratoma contains cells from all three germ layers. Claim 46 is directed to the teratoma of claim 44, wherein the teratoma is derived from a cloned ungulate cell. Claim 47 is directed to the teratoma of claim 46, wherein the teratoma is derived from a cloned bovine cell.

Anderson *et al.* teach the implantation of inner cell masses and embryonic discs from bovine and porcine blastocysts under the kidney capsule of nude mice (see *Abstract*). Specifically, Anderson *et al.* teach that athymic BALB/C mice were used as hosts for embryonic grafts. The mice were implanted with two to four inner cell masses, embryonic discs, egg cylinders or intact Day 8 in vitro-derived bovine blastocysts which were deposited under the kidney capsule (see p. 233, 2.2). Anderson *et al.* teach that the mice were killed by cervical dislocation 8 weeks after transplantation and the tumors were excised from the kidney. These tumors were classified as benign teratomas, or malignant teratocarinomas. Selected tumors were stained immunohistochemically for the presence of various markers (see p. 233, 2.3). Anderson *et al.* teach that the representation of cell types of ectodermal, mesodermal and endodermal origins in the bovine and porcine tumors was somewhat more restricted than from murine embryonic tumors (see *Abstract*).

Accordingly, Anderson *et al.* anticipate claims 38, 42, 44, 45, 46 and 47.

Conclusion

No claim is allowed. Claims 1-14, 20-28, 33, 39-41, 43 appear to be free of the cited prior art of record, as the prior art of record fails to teach or suggest method of testing immune compatibility of cloned cells of tissues in an animal model comprising obtaining a cell from a donor animal, transferring the nucleus from the cell into a recipient oocyte or other suitable recipient cell to generate an embryo, isolating an embryo having at least one cell, an embryonic disc, and/or stem cell from said embryo, injection the embryo, disc, and/or stem cell into a donor animal at the same time as a control embryonic disc and/or stem cell; and examining the injection sites for teratoma formation; and methods for generating immune compatible tissues for transplantation comprising obtaining a donor cell from an intended transplant recipient, transferring the nucleus from said cell into a recipient oocyte or other suitable cell to generate an embryo or fetus, isolating from the embryo or fetus a cell of the type required for transplantation, and engineering a tissue from the cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Deborah Crouch

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